DOCKET NO.: ISIS0053-100 (RTS-0182)
Serial No.: 09/731,457

PATENT
Filing Date: December 6, 2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: **Popoff and Wyatt**

Serial No.: **09/731,457** Group Art Unit: **1635**

Filed: **December 6, 2000** Examiner: **James Schultz**

Title: **ANTISENSE MODULATION OF DAMAGE-SPECIFIC DNA BINDING PROTEIN 1, P127 EXPRESSION**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

DECLARATION UNDER 37 CFR §1.132

I, Dr. Susan Freier, a citizen of the United States, residing at 2946 Renault Street, San Diego, CA 92122, state and declare as follows:

JDS (considered) 6-21-04

1. I hold a B.A. in Mathematics (1972) from Carleton College, Northfield, Minnesota and a Ph.D. in Chemistry (1976) from the University of California, Berkeley, California.

2. I have been employed by Isis Pharmaceuticals, Inc. ("Isis"), for about fourteen years. Isis, the assignee of the above-identified patent application, specializes in oligonucleotide technology and uses the latest in bioinformatics programs to identify sites on selected genes for oligonucleotide screening. I am presently the Executive Director of antisense lead identification at Isis. In my position I am responsible for a number of projects. I lead a project utilizing antisense oligonucleotides for functional genomics of novel targets, including the use of computational genomics to characterize target RNAs and their variants, rapid throughput screening to identify active antisense oligonucleotides for novel targets, and Q-RT-PCR and microarrays for expression analysis. I also lead a project for determining microRNA function in mammals, including

the use of computational identification of miRNAs and miRNA targets and the use of functional genomics to characterize miRNA biology and identify therapeutic applications of modulation of miRNA activity. In addition, I lead a group charged with the identification and characterization of novel mechanisms for antisense oligonucleotides, including the use of computational genomics to identify mRNA variants, alteration of RNA processing, evaluation of siRNA and miRNA mechanisms. Another project I am responsible for involves biophysical and biochemical evaluation of novel antisense oligonucleotides, including the evaluation of thermodynamics and kinetics of hybridization to oligonucleotide and large structured targets, evaluation of the biochemical properties of novel oligonucleotides, characterization of antisense activity in cell assays, and protein-oligonucleotide binding.

3. As early as 1995, I performed and supervised experimentation employing oligomeric compounds and inhibition of mRNA expression. My work has involved designing assays to screen oligomeric compounds against specific genes as well as interpreting the results from such assays. I have authored or co-authored numerous scientific journal articles regarding the same. I am an expert in the art of antisense technology and oligonucleotide screening. A copy of my *curriculum vitae* is attached as Exhibit 1.

4. I have read the Office Action dated January 5, 2004 and understand that claims 1, 2, 4-10 and 12-15 of the above-identified application have been rejected as allegedly being obvious over the following combination of references: Dualan *et al.*, U18299 nucleotide sequence and abstract ("*Dualan*"); Taylor *et al.*, 1999 *Drug Disc. Today*, 4(12):562-567 ("*Taylor*"); Baracchini *et al.*, U.S. Patent No. 5,801,154 ("*Baracchini*"); Hayes *et al.*, Mol. Cell. Biol., 1998, 1:240-249 ("*Hayes*"); and Krishnaoorthy *et al.*, Biochem., 1997, 36:960-969 ("*Krishnaoorthy*"). I make this declaration to rebut the unsupported statements in the Office Action regarding the motivation for combining the cited references and the alleged reasonable expectation of success by one of skill in the art for inhibiting the expression of any particular gene or mRNA with oligomeric compounds based only upon a given gene sequence. In particular, I make this declaration

to question the statement in the Office Action that the lack of details relating to *Taylor's* experimental design is compensated for by *Baracchini*.

5. One of skill in the art would not be motivated to combine the cited references in the manner set forth in the Office Action. The only motivation identified in the Office Action for inhibiting human damage-specific DNA binding protein 1, p127 is purported to be provided by Dualan. Indeed, the other cited references do not so much as even mention human damage-specific DNA binding protein 1, p127, let alone inhibiting such protein. Dualan, however, simply reports the nucleotide sequence of human damage-specific DNA binding protein DDB p127 subunit. Dualan also does not teach or suggest inhibition of human damage-specific DNA binding protein DDB p127 subunit in any particular manner. Thus, even if one skilled in the art desired to inhibit the damage-specific DNA binding protein DDB p127 subunit reported in Dualan, there is no motivation to pursue oligomeric compound-induced inhibition rather than antibodies, peptide/protein inhibitors, or small molecules. Thus, one skilled in the art desiring to inhibit the activity of a particular protein generally has many options to pursue, only one of which is via oligomeric compounds.

6. It is not currently possible to predict the level of inhibition of expression achieved against a particular gene with any particular oligomeric compound prior to carrying out the appropriate experiments. It is also not reasonable to expect for any particular gene or mRNA that any number of oligomeric compounds exhibiting at least 60% inhibition of expression, as stated in claim 1 of the present application, will be obtained.

7. For example, as indicated by Exhibits 2 (inhibition of human tyrosine kinase, non-receptor, 1 mRNA expression in T-24 cells) and 3 (inhibition of rat urate anion exchanger 1 mRNA expression in Rin-M cells), 80 oligomeric compounds (each being 2'-O-methoxyethyl gapmers) were examined for their ability to inhibit expression (please note that the results are presented as % expression of the control). Referring to Exhibit 2, no oligomeric compounds inhibited expression by at least 60%. Referring to Exhibit 3,

again, no oligomeric compounds inhibited expression by at least 60%. In my opinion, the results obtained for human tyrosine kinase, non-receptor, 1 and rat urate anion exchanger 1 represent a potential outcome of any target screen. It is *not* presently possible to predict *before* the appropriate experiment is performed, which targets will generate oligomeric compounds that will have the desired level of inhibition of expression.

8. This evidence demonstrates that one skilled in screening of oligomeric compounds cannot, *a priori*, reasonably expect a particular level of inhibition (i.e., such as at least 60%) of a gene or mRNA simply because methods of screening oligomeric compounds are available and/or routine. The statements in the Office Action regarding reasonable expectation of success are neither accurate nor capable of being supported.

9. Each gene is unique. For instance, if one skilled in the art achieved at least 66% inhibition in the expression of a first gene with oligonucleotides that are specific to the first gene, one skilled in the art *would not* reasonably expect success in achieving at least 66% inhibition in the expression of a *different* gene with a different set of oligomeric compounds that are targeted to the different gene or mRNA. The level of inhibition of expression that is observed for one target has no bearing on the level of inhibition of expression expected for a different target.

10. *Taylor* is a review article that makes unsupported assertions about the ease of identifying target sites on *any* gene for oligonucleotides that, upon binding to the target, can inhibit gene expression. The determination of target sites on a gene that permits one to identify suitable, highly inhibitory oligonucleotides for that gene is not a process that can be predicted to be easy or simple, based merely upon the identification of the gene sequence of the target gene or even a suggestion that inhibition of a particular gene may be desirable.

11. *Taylor* purports that only 3-6 oligonucleotides need to be screened in order to find an oligonucleotide that inhibits expression with 66-95% efficiency. *Taylor*, however, has numerous deficiencies that seriously impact its ability to teach one skilled in the art

how to screen for such active oligonucleotides. For example, *Taylor* fails to identify the chemical modifications that make the oligonucleotides reported therein chimeric. In addition, *Taylor* fails to identify any bioinformatics program reported therein (particularly the one that apparently can screen as few as 6-9 oligonucleotides to find one that inhibits gene expression with 66-95% efficiency) by name. Indeed, I am not aware of any such computer program. Further, *Taylor* even fails to identify the manufacturer of such a bioinformatics program reported therein. *Taylor*, rather than actually teaching one skilled in sufficient details that would actually allow one skilled in the art to carry out screening methods with such fantastic results, simply refers to "unpublished data." *Taylor* also fails to teach how such results may be attained manually. Thus, *Taylor* acts only as general guide for screening oligomers and does not provide any details sufficient for one skilled in the art to carry out any particular methodology. Indeed, I am unaware of any algorithm or methodology presently available that would enable one either to predict *a priori* whether a particular level of inhibition (i.e., such as at least 60%) of a gene or mRNA will occur.

12. As one of skill in the art and as an author of over 75 scientific references, the mere fact *Taylor* was published in a peer-reviewed journal *does not* mean that the reference teaches how to practice that which it purports to teach.

13. *Baracchini* does *not* compensate for the many deficiencies discussed above in relation to *Taylor*. *Baracchini* fails to teach how to select target regions for the 3-6 oligonucleotides to be screened to be able to find an oligonucleotide that inhibits expression with 66-95% efficiency. *Baracchini* also fails to provide the identity of the computer program referred to in *Taylor*. *Baracchini* further fails to discuss how such results may be attained manually. I could not practice the methods of selecting target regions described in *Taylor*, even in view of *Baracchini*.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the

like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 3-Jun-04 By: _____

Susan Freier, Ph.D.

Attachments:

Curriculum vitae of Dr. Susan Freier

Exhibits 1, 2 and 3